# A century of bias in genetics and evolution

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Mendel proposed that the heritable material is particulate and that transmission of alleles is unbiased. An assumption of unbiased transmission was necessary to show how variation can be preserved in the absence of selection, so overturning an early objection to Darwinism. In the second half of the 20th century it was widely recognised that even strongly deleterious alleles can invade if they have strongly biased transmission (i.e. strong segregation distortion). The spread of alleles with distorted segregation can explain many curiosities. More recently, the selectionist-neutralist duopoly was broken by the realisation that biased gene conversion can explain phenomena such as mammalian isochore structures. An initial focus on unbiased transmission in 1919, has thus given way to an interest in biased transmission in 2019. A focus on very weak bias is now possible owing to technological advances, although technical biases may put a limit on resolving power. To understand the relevance of weak bias we could profit from having the concept of the effectively Mendelian allele, a companion to the effectively neutral allele. Understanding the implications of unbiased and biased transmission may, I suggest, be a good way to teach evolution so as to avoid psychological biases.

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## INTRODUCTION

I am somewhat reluctant to admit that when I first met genetics as a subject I was, shall we say, less than enthusiastic. Some monk far away (in time and space) bred some peas and he found that heterozygotes mated to heterozygotes leave three of one sort to one of the other. How interesting (I didn't think). In part my lack of enthusiasm was understandable. I knew about meiosis - and had been made to learn the names of all the stages – and when you know about mutations, DNA, chromosomes and meiosis, which of course Mendel didn't know, then 3:1 ratios are simply an

obvious consequence (assuming you add in a hefty dose of dominance). I similarly couldn't see the excitement in a Punnett square – it just seemed too simple.

The seemingly trivial result from Mendel, however, presents a circumstance possibly unique in science, one in which a central theory requires a particular parameter to be a very particular value. The parameter in question is the extent of deviation alleles receive in meiosis away from 50:50 segregation in heterozygotes. In this opinion piece, I note that, both at the start of the history of The Genetics Society and now, this parameter was and is of great importance. A century ago it was important because the realization that inheritance is particulate and meiosis is typically "fair" (i.e. no deviation from 50:50) has important theoretical consequences for the preservation of variation and, in turn, the role of selection. Now it is of interest because it seems clear that, at least in some genomes, there are regular deviations from 50:50 and that this non-Mendelian transmission probably resolves recent debates between selectionists and neutralists (e.g. the isochore debate) in favour of neither. It may even explain, at least in some instances, why speciation happens. However, our abilities to resolve subtle but potentially important biases is currently facing technical limitations owing to methodological biases. More generally, the relationship between transmission bias (or lack thereof) and our understanding of evolution, highlights the importance of having a strong rooting of evolutionary genetics in molecular and transmission genetics: now more than ever, we need all branches of genetics to be integrated under one umbrella. The same intimate link between genetics and evolution is for the most part ignored in UK school teaching. Understanding of the role of bias in transmission is, I suggest, a helpful way of explaining the relationship between the two, so overcoming psychological biases that can be an impediment to learning owing to cognitive dissonance (Festinger, 1957 ).

**Fitness isn't so important if inheritance isn't Mendelian**

Mendel's major insight was that inheritance is particulate. Heterozygotes have two different versions of these particles – he didn't call them alleles, but would do so now. Let us ask about the population genetics of an imaginary sexual species that is randomly mating just by considering what the fate of these alleles will be. I'll suppose there are only two such alleles and neither confers a fitness advantage over the other. I'll need to know something else: the rate at which my two particles are transmitted from heterozygotes to the next generation. Let me suppose that for one of them this rate is $0.5 + k$ and so for the other the rate is $0.5 - k$ (with $k$ greater than or equal to zero). Now let me ask about what is going to happen as I forward project in time so as to

determine what their longer-term fates will be. The oddity is that unless $k$=0, one of the two alleles will go to fixation because of the transmission bias: the allele with transmission rate 0.5 + $k$ is the winner in this game.

This is a mathematically simple result. Neither allele affects your fitness but owing to segregation distortion, i.e. by being transmitted at greater than Mendelian rates ($k$>0), one allele will spread through the population regardless. Although mathematically simple, this is also a profound result. That Punnett square and those 3:1 ratios, all assume not simply particulate inheritance, but that $k$=0 so that alleles are transmitted at equal rates through meiosis. The Punnett square works because each box in the square has the same probability. Importantly, when we add in fitness into the equation, only when $k$=0 do we find that the only parameter that matters is the effect on fitness. If this isn't true, natural selection operating on organismal fitness would be just one player in the game. Indeed, alleles that are deleterious can spread so long as $k$>0 and the larger the value of $k$, the more deleterious the allele can be (Bruck, 1957; Hiraizumi *et al*, 1960; Prout, 1953; Sandler and Novitski, 1957). If $k$>0, we wouldn't be talking about survival of the fittest (which focuses on phenotypic effects of alleles), but instead on persistence of the allele with the ability to transmit at high rates through meiosis.

**The $k$>0 problem and Jenkin's swamping arguments are similar**

The problem of the impotence of natural selection when $k$>0 is not greatly dissimilar to the problem raised by the electrical engineer Fleeming Jenkin (Jenkin, 1867) in objection to the notion of natural selection. Jenkin thought inheritance was blending rather than particulate, but the core problem is the same. Jenkin's swamping argument, as usually presented (for critique see Morris, 1994), was that if inheritance was blending, then new advantageous traits would have difficulty in spreading by selection, as selection had to fight against the mode of inheritance and variation will be lost. Jenkin considers the case of a shipwrecked white man on an island of (which he assumed to be inferior) "*negroes*". He presumes that "*our shipwrecked hero would probably become king; he would kill a great many blacks in the struggle for existence; he would have a great many wives and children, while many of his subjects would live and die as bachelors ... In the first generation there will be some dozens of intelligent young mulattoes, much superior in average intelligence to the negroes. We might expect the throne for some generations to be occupied by a more or less yellow king; but can any one believe that the whole island will gradually acquire a white, or even a yellow population?*"(Jenkin, 1867). Jenkin's biases here are self-evident. Moreover, ironically, Jenkin did in fact make a miscalculation in a numerical example he presented (Davis, 1871) (for discussion see Bulmer, 2004). Nonetheless, the point remains that selection can have a

problem if it must fight against the mode of inheritance and, unless there is a high mutation rate, variation will tend to be lost.

It was only a decade before the founding of The Genetics Society, that Hardy (1908) and Weinberg (1908) derived their striking result that under unbiased Mendelian inheritance variation was preserved and, so the story goes, evolution by natural selection was rescued as a concept (Morris, 1994). But, this intellectual rescue requires that our transmission parameter $k$, take one value, i.e. zero. Normally in science this would be regarded as special pleading. Typically, if you construct a mathematical model, you look to see how broad the parameter space is for your model to work. If this space is small, then your model is looking a bit flimsy. If it requires one value alone, it is usually dismissed out of hand: in an infinitely large world of possible parameter values, to demand that one value alone is required is a pretty remarkable requirement. Indeed, I know of no other model in science of any flavour where such an important body of theory starts by presuming the one value of a parameter necessary for the models to work. But this is what the vast bulk of population genetics does and is the cornerstone of why we think selection (organismic fitness) is so important.

Above I suggested that if $k$ is not zero we wouldn't be talking about survival of the fittest. I'm not sure we would be talking at all. Could a complex meiotic species viably exist if segregation is consistently non-Mendelian? It is quite hard to see how any meiotic species could adapt to changing conditions if the primary determinant of the fate of an allele is not its effect on fitness but is instead its transmission rate through meiosis. You might imagine that such species would adapt by preventing heterozygosis-associated transmission (e.g. by being asexual, by inbreeding or by forcing uniparental inheritance). But several problems present themselves. First could a species with non-Mendelian inheritance at all loci evolve modifiers to control non-Mendelian inheritance? There is a large literature on modifiers to control the way genes are inherited (see Feldman and Otto, 1991), but they start by presuming that the modifier is itself Mendelian. As a philosophical enterprise it would be intriguing to see how the world might look differently. The second problem, is that even if selection of some form could favour asexuality/selfing/uniparental inheritance then the lineages become actually or effectively asexual. But asexual multicellular lineages tend to go extinct and non-meiotic lineages tend not to be multicellular. Prokaryotes (eubacteria and archaea) have, for example, been around for several billion years but never evolved complex multicellularity (for discussion as to why see Lane, 2014; Lane and Martin, 2010; Lane and Martin, 2016; Lynch and Marinov, 2016; Lynch and Marinov, 2017; Lynch and Marinov, 2018).

**Why might $k=0$?**

The argument that, for evolution by natural selection to be a common and viable mode of evolution $k=0$ is necessary, might be misinterpreted as meaning that evolution by natural selection is somehow unlikely. Before anyone suggests that I am advocating some strange argument for the existence of a parameter-fixing god, I am not. That $k = 0$ is not some miracle. It follows as the default value if nothing is happening except for meiosis. We don't need special pleading to address this problem. Put differently, that the chromosomal theory of inheritance (Boveri, 1904; Sutton, 1902; Sutton, 1903) so neatly explained Mendelian ratios (Carothers, 1913), not only explains why the chromosomal theory came to be accepted (Crow and Crow, 2002), but also, in turn, provides a defence for considering Mendelian ratios as the default.

This being said, others have considered the problem of how $k=0$ might evolve, were $k=0$ not the default (see e.g. Crow, 1991; Eshel, 1985). Leigh conjectures about a parliament of the genes where majority opinion has sway (Leigh, 1971). While such language may be attractive, what this means in practice is less then transparent. Consider, for example, modifiers that suppress segregation distorters. The difficulties here are multiple. First, if the suppressor is costly, a balance between the persistence of the distorting allele and the suppressor can be found (unpublished), so Mendelian segregation needn't be the equilibrium solution. Second, such models presume nearly all genes, the suppressive modifiers included, are Mendelian and the locus with $k>0$ is the exception. What would happen in a system in which non-Mendelian inheritance was the default is to the best of my knowledge unknown. Third, such an argument may be unnecessary. Autosomal alleles with $k>0$ can rapidly spread to fixation if the distorter homozygotes aren't of too low fitness. At fixation, as everyone has the distorting allele, there is no distortion (at least at that locus for the time being). If the distorter has a high value of $k$ and was sex-linked the population could go extinct owing to a dearth of one of the two sexes (such an X v Y or Y v X distorter will result in heavily biased sex ratios). Either way, the extant populations have no distortion.

Thus, while $k=0$ looks like a fine democratic outcome, it could be either the default or the consequence of an inability of any system to do much about rapid spread. Indeed, in fungi, the species with segregation distorters tend to be more inbred ones (van der Gaag *et al*, 2000). Inbreeding slows the transit of distorters making it more likely that we will observe them as they slowly proceed to fixation (van der Gaag *et al*, 2000). We can then extrapolate to suppose that absence of distortion in outbred fungi is a consequence of rapid spread to fixation of such

distorters rather than their absence. Similarly, the well described autosomal distorters (*SD* in flies, *t*-complex in mice) tend to be homozygous steriles or lethals, either owing an intrinsic consequence of the mechanism of action or owing to linked alleles. This low homozygous fitness prevents their fixation and thus makes it easier for us to discover them. How often then are populations affected by very rapidly spreading segregation distorters with high homozygous fitness? Additionally, these and other well described meiotic drive genes are two tightly linked loci (toxin and antidote)(Lyttle, 1991) and so are probably hard to mutationally assemble. This being said, there are much simpler modes of transmission distortion (e.g. GC biased gene conversion, of which more later). Nonetheless, I'm not convinced we need a special case to explain why $k$=0.

**The slow rise of non-Mendelian genetics.**

If in the early part of the twentieth century deviations from Mendelian inheritance were not given much prominence, it is most likely because most instances of classical single locus conditions are Mendelian (or at the very least, very hard to distinguish from Mendelian). The rise of the chromosomal theory of inheritance (Boveri, 1904; Sutton, 1902; Sutton, 1903) and with it the logic of Mendelian segregation ratios (Carothers, 1913), no doubt also played a role in seeing Mendelian inheritance, quite correctly, as the default mode of inheritance. Nonetheless, deviations from classical Mendelian inheritance did crop up in the early decades of the last century. Mice homozygous for the Yellow allele, for example, are never witnessed in heterozygote x heterozygote crosses (Castle and Little, 1910). While sometimes appearing in textbooks as exceptions or extensions to Mendelian inheritance, these could just as well be viewed as Mendelian with respect to transmission but with early viability selection. Indeed, had this been post-natal inviability, this is probably how they would be classified. Similarly, uniparental cytoplasmic inheritance was discovered early (this is usually jointly credited to Correns and Baur, but Baur seems to have been clearer on the subject (see Hagemann, 2000)). From a population genetics point of view uniparental inheritance, although non-Mendelian, is not the same as biased transmission, as on the average any given allele is transmitted 50% of the time – it just happens to be 100% from one sex and 0% from the other, rather than 50% from each. Similarly, unbiased gene conversion is unlikely to have a deterministic effect: for every case that a locus is subject to 3:1 gene conversion in a tetrad there can be an equal but opposite 1:3 event (Gutz and Leslie, 1976). None of these phenomena thus disturb the notion of unbiased transmission.

The earliest consideration of the possibility of biased transmission that I am aware of is pre-Mendelian. Darwin thought, at one point, that gemmules moved from the body to the gonads

and these formed the basis of inheritance (Darwin, 1868) (he often changed his mind about inheritance, possibly owing to Jenkin's objection). He considers the problem of biased transmission of such gemmules as possibly explaining increases in the numbers of body appendages. He conjectures "*As the cells of adjoining or homologous parts will have nearly the same nature, they will be liable to acquire by variation each other's elective affinities; and we can thus to a certain extent understand such cases as a crowd of horns on the heads in certain sheep, of several spurs on the leg, and of hackles on the head of the fowl*" (p393). However, as this was part of a longer narrative based on the incorrect notion of pangenesis, it can hardly be counted a major contribution to the field, although it does highlight that thinking about bias in transmission is not new.

In the early post-Mendelian era (i.e. after circa 1900-1930) there were several parallel discoveries of deterministically biased transmission (e.g. Correns, 1902; Gershenson, 1928; Heribert-Nilsson, 1920; Metz and Moses, 1923; Morgan *et al*, 1925), including sex ratio distorters (Simmonds, 1923a; Simmonds, 1923b; Simmonds, 1926; Simmonds, 1928) with one such observation possibly as early as 1911 (Federley, 1911; Federley, 1936). For consideration of Renner's extensive work on non-Mendelian inheritance in *Oenothera* see Sturtevant (1926). While the genetics is often well described, consideration of the population genetical impact of such biased transmission was, however, often a little confused. Consider, for example, Gershenson's analysis of an X-linked meiotic drive gene causing all female progeny in *Drosophila* (Gershenson, 1928). He argues that "*since it exists in the natural population it is probably useful, or at least harmless for the evolution of the given Species*". This is the usual backwards Darwinian logic – if it is observed it must be beneficial. Strikingly he then also notices that "*the extension of this gene among the wild population must be expected even without the action of positive selection. Usually a sex-linked gene is transmitted by the father to a half of the descendants only, whereas here all or nearly all the flies receive it with the X-chromosome of the father; this favors its extension*". Although confused, this does seem to be the first understanding that alleles can deterministically spread owing to biased transmission.

If Gershenson was simultaneously confused but also perspicacious enough in realising that biased transmission alone could lead to invasion, Haldane (1932) a few years later was characteristically clearer, but dismissive of the potential importance of biased transmission. He considered certation, the biased transmission of certain alleles of a heterozygote through pollen (Heribert-Nilsson, 1920; Heribert-Nilsson, 1923). He comments that because of such a bias, a plant is "*at the mercy of its pollen grains*", noting that an allele could spread even if mildly deleterious or unable to spread even if advantageous to the plant, if it was uncompetitive in pollen. Curiously, however,

while relating that he once considered the phenomenon to be of "*overwhelming importance*", he concludes by dismissing it, arguing that selective intensity increases only very slowly with intensity of competition (see also Leigh's afterword to the 1990 edition of *The Causes of Evolution* (Leigh, 1990)). For animals he considers the phenomenon irrelevant as sperm don't express their haploid genotype. One wonders if his view would have changed were he made aware of Gershenson's work.

While the idea that biased transmission enables alleles to invade a population even if deleterious to the bearers of such alleles appears not to have gained great traction after Haldane's considerations, like all good ideas it resurfaced independently (or so I presume) over a decade later. Östergen (1945) argued that non-Mendelian B chromosomes could be genomic parasites. Noticing their ability to be present in more progeny than they would be were they to segregate in Mendelian ratios he argues that "*it is obvious that they would get a considerable spread even if their effect on the plants was quite unfavourable*", concluding that "*they need not be useful to the plants*, *they need only be useful to themselves*". Here he was arguing against Cyril Darlington who took the standard Darwinian line that B chromosomes must have a utility (i.e. increase organismic fitness) (Darlington and Thomas, 1941), conjecturing roles in nucleic acid metabolism. In this context, striking contrast can also be made with Östergren on the one hand, and Lewis (1941) who just a four years earlier had mathematically modelled the logically comparable phenomenon of cytoplasmic male sterility (CMS). The mitochondrial mutations that induce CMS are also one class of selfish genetic element, the general term for alleles that invade owing to transmission bias (of any flavour) whilst potentially being deleterious. In CMS the mutation sterilizes male tissue, so distorting the hermaphroditic plant's reproductive investment towards egg production away from pollen production. As mitochondria are maternally transmitted, this enables the mutation to spread in the population, even though it is deleterious, but also creates the conditions for the spread of suppressor mutations. While Östergren's arguments were all verbal, Lewis (1941) lays out the maths of CMS, notes how broad the conditions for spread are, but simultaneously conjectures what the advantage must be to the plant to have such alleles (he conjectures a reduction in selfing). He doesn't notice that the allele could be deleterious and still spread, even though it is implicit in the maths.

While Östergren is sometimes thus credited as one of the first to provide a clear argument to the effect that alleles can be deleterious and still spread if they have a transmission advantage, the importance of the paper may be more profound in retrospect than it was at the time. According to the Web of Science the paper has been cited only a little over 100 times, initially only within the

B chromosome literature. Indeed, it wasn't until 1980, when Cavalier-Smith drew the attention of the proponents of the selfish DNA hypothesis to the fact that they should have acknowledged Östergren (Cavalier-Smith, 1980), that it makes its way out of the more specialist literature. Evidence would suggest that instead the discussion of Sandler and Novitski (1957), a further decade on from Östergren, is perhaps the first to provide an influential assessment of the evolutionary implications of the problem of biased transmission (and coined the term meiotic drive). This has been cited over 350 times. They rely on the rarely cited mathematical model by Prout, an appendix to the rarely cited Dunn (1953). For fuller mathematical treatment see Hiraizumi et al. (1960). In part the difference in impact may lie in the accessibility of the journals concerned (*American Naturalist* as opposed to *Botaniska Notiser*) rather than any important difference in what was being argued.

There is a history to be written about the rise of the understanding that alleles can spread and be deleterious, about the importance (or lack thereof) of Haldane's dismissal and the influence (or lack thereof) of Östergren's insights. Central to any such history would be Hamilton's insights and the refocusing of the conceptualization of evolution at the allele level (popularised a decade later by Dawkins). Hamilton in his sex ratio paper (Hamilton, 1967), for example, is transparent that sex ratio distorting chromosomes (X v Y or Y v X distorters) can invade and either potentially send a population extinct or provide the conditions favouring alleles that suppress the distortion.

Core to the new view of alleles with biased transmission is that, while they can both spread and be deleterious, they can also thus create conditions for suppressors (Hiraizumi *et al*, 1960; Östergren, 1945), hence cause genetic conflicts (Burt and Trivers, 2008; Cosmides and Tooby, 1981; Hurst *et al*, 1996; Östergren, 1945; Werren, 1987). Here again, Östergren (1945) was clear arguing that we expect plants to evolve suppressors of B chromosomes and for the B chromosomes in turn to counter-adapt. He argued that "*If the fragments are unfavourable to the plants, there should tend to accumulate in the population factors of a type inhibiting their continued spread*" and that "*This tendency to the evolution of an »eliminative system» in the normal complement would be counteracted by a tendency to the evolution of an »accumulative system» in the fragment itself. Selection would favour fragments with a more efficient spreading mechanism*". Haldane's understanding that advantageous alleles cannot invade if they suffer biased transmission that acts against them, suggests that he would easily have understood the same concepts, he just didn't pick up the ball and run with it, so to speak.

Selfish elements and the response they provoke can help explain all sorts of apparently strange phenomena, although historically conjecture has been more prominent than evidence, although

that is changing. In particular, the notion that selfish elements spread because they can be deleterious, makes them attractive candidates for mediators of hybrid disruption (Frank, 1991; Hurst and Schilthuizen, 1998; Hurst and Pomiankowski, 1991), for which striking evidence now exists (Hauschteck-Jungen, 1990; Phadnis and Orr, 2009; Tao *et al*, 2001) (see for reviews see (McDermott and Noor, 2010; Patten, 2018; Presgraves, 2010)). As there are multiple reviews on selfish elements and genetic conflicts (Agren and Clark, 2018; Burt and Trivers, 2008; Hurst *et al*, 1996; Werren, 2011; Werren *et al*, 1988), I'll not indulge at length save to provide one exemplar, the strange case of alleles that select for ever earlier death of embryos.

At first sight, selection should never favour alleles that kill the embryos they are in. But selfish elements are odd. The *t*-complex in mice is a meiotic drive gene complex on chromosome 17. It appears that an intrinsic component of the way drive acts is that in homozygous form it causes males to be sterile (for discussion see Lyon, 1992; Lyon, 2003). The drive chromosome is held in the population by a balance of drive in heterozygotes increasing its frequency and homozygous sterility preventing it from going to fixation. The species in question is a mouse. Mice have continual supply of resources as embryos. But what is the point in investing in an embryo that will grow up to be infertile? If these sterile progeny could be killed *in utero*, resources could then be freed up for other progeny. Thus we have the strange circumstance of the evolution of embryonic mortality in which mutations act to kill early rather than to prevent such mortality (Charlesworth, 1994a). As expected, the lethal alleles are in linkage disequilibrium with the *t*-complex and are recessive (Charlesworth, 1994a).

**Can *k*>0 explain isochores?**

Examples usually considered in the context of selfish elements have very strong distortion phenotypes: nearly all the offspring in Gershenson's X-linked drive example were male and nearly all progeny of male heterozygotes for *t*-complex or *SD* inherit the distorter. Less experimental effort has been given to weak distorters, in no small part because these are harder to detect. Recent technological innovations, notably whole genome sequencing permitting affordable parent-offspring sequencing, is now changing matters. Here I am thinking in particular of biased gene conversion (BGC)(Brown and Jiricny, 1988; Lamb, 1984; Lamb, 1985) (for reviews see (Duret and Galtier, 2009; Marais, 2003)).

In meiosis when one strand invades another from an homologous chromosome a heteroduplex is formed. This can be associated with crossing over or non-crossover recombination. This heteroduplex is unusual double stranded DNA as there will be mismatches at any sites that are

different between the two homologs. The question is what to do with the mismatches. Let's suppose we have a T:C mismatch. One possibility is to toss an unbiased coin to decide whether to replace the C with an A or the T with a G. Both will give a gene conversion event, but there will on the average be no bias to this process. We will see a 3:1 segregation in any given tetrad, but at the population level, with the T->C rate the same as C->T rate, there is no effect on allele frequencies. But what if the process is biased? Bengtsson (1985) has suggested there may be good reason for it to evolve to be biased. Mutation is more commonly in the direction GC->AT, so at a T:C mismatch, it is more likely that C is the ancestral allele and T the more recent mutant. As most mutation is deleterious, evolution should favour the C over the T at the mismatch, thereby correcting a mutation. The best evidence we have from mammals and birds is that, indeed, gene conversion can be biased in favour of GC alleles over orthologous AT alleles. Such a bias is seen in humans (68% AT->GC)(Halldorsson *et al*, 2016; Lesecque *et al*, 2013; Williams *et al*, 2015) and flycatchers (59% AT->GC)(Smeds *et al*, 2016). BGC is also present in honey bee (Wallberg *et al*, 2015) but possibly absent in *Drosophila* (Robinson *et al*, 2014). Note that the numbers here reflect the degree of distortion when biased gene conversion happens at a given site: the net effect at any given site depends on this and the rate at which the site is subject to gene conversion. The percentage of a markers in a genome associated with gene conversion tracks in any given meiosis varies from ~2% in yeast to only ~0.005% in *Arabidopsis* (Liu *et al*, 2017), but hotspots can exist. The population genetics of biased gene conversion is similar to that of meiotic drive (Gutz and Leslie, 1976), excepting that drive typically happens in every drive heterozygote, while biased gene conversion requires the conversion tract, and heteroduplex, to form around the GC:AT heterozygous site. Just as drive alleles can be deleterious, so too in some cases the favoured allele can be deleterious and such a process could lead to the driven degradation of domains of high recombination.

Importantly, this process of biased transmission provides our best current explanation as to why our genome has blocks of high GC and others with low GC (isochores) and why non-recombining chromosomes and centromeres are AT rich (Eyre-Walker, 1993). The high GC domains are crucially domains of high recombination (Duret and Galtier, 2009; Fullerton *et al*, 2001) in which the fixation process, but not the mutation process, is biased towards GC alleles (Duret *et al*, 2002; Lercher *et al*, 2002). AT rich regions, by contrast, are low recombination domains in which there is no evidence for a fixation bias and appear to be closer to mutational equilibrium, mutation being GC->AT biased. Thus, the high GC domains are not explained by mutation bias and drift (i.e. not the neutralist model). Possible neutralist models include the notion that the mutation bias varies around the genome, possibly associated with replication time. This model, however,

predicts a concordance between the frequency profile of rare and fixed mutations and, assuming compositional equilibrium, that the numbers of GC->AT and AT->GC SNPs should be equal (Eyre-Walker, 1999). However, this concordance isn't seen (Duret *et al*, 2002; Lercher and Hurst, 2002; Lercher *et al*, 2002).

Selectionist models, that are consistent with this fixation bias, are in principle hard to discriminate from a biased gene conversion model. Such weak selection models suggest that domains of high GC may simply reflect a greater efficiency of selection in domains of high recombination (Charlesworth, 1994b) owing the reduced Hill-Robertson interference. A weakness of many such models is that the typically don't specify why, exactly, an AT->GC SNP is selectively favoured, even in non-coding DNA far from gene bodies, they just presume that it could be. In this regard, the model could equally well be consistent with a model supposing that recombination was associated with domains of low GC. Some suggest that increased GC content is an adaptation to higher temperatures (Bernardi and Bernardi, 1986), but the overall validity of this is questioned (Eyre-Walker and Hurst, 2001), not least because thermophilic prokaryotes aren't GC rich (Galtier and Lobry, 1997; Hurst and Merchant, 2001) and isochores aren't unique to homeotherms (Hughes *et al*, 1999). Fixation by selection also implies a genetic load associated with their creation and maintenance. It is then curious that isochores are witnessed in organisms with low effective population sizes and low variance in offspring numbers (mammals), where selection is expected to be weakest and load least tolerable, but not seen in fruit flies and yeasts. It is also unclear why the evolution of GC content correlates much more strongly with male recombination than female recombination rates in humans (Duret and Arndt, 2008) (see also Popa *et al*, 2012). It is also questionable as to whether selection can explain the strength of any GC-recombination correlation (Duret and Arndt, 2008), although a complicating factor is that, at least in yeast, high GC can predispose to high recombination rates (Kiktev *et al*, 2018; Marsolier-Kergoat and Yeramian, 2009).

Biased gene conversion, by contrast provides a better specified and more parsimonious model. It requires no increased genetic load, explains a fixation bias, why this bias is associated with domains of high recombination, and importantly, why high recombination is associated with high GC, this being the observed direction of the transmission bias. It also provides a parsimonious explanation as to why GC content variation is declining in some mammals (Duret and Arndt, 2008; Duret *et al*, 2006; Duret *et al*, 2002). It could potentially explain the sex-specific nature of the GC - recombination correlation (Duret and Arndt, 2008) but this has yet to be verified. More generally, one can indeed argue that given the observed gene conversion bias, the evolution of isochores

becomes near inevitable so long as recombination is itself concentrated in certain genomic domains. Thus, what was pitched as the ultimate neutralist-selectionist battle (Eyre-Walker and Hurst, 2001), is most likely resolved by a third class of explanation: biased transmission (Duret and Galtier, 2009).

Is this really a third class of explanation? Some suggest that BGC is a neutral process (Galtier *et al*, 2001). But the bearers of the advantaged allele can be at a disadvantage and the maths doesn't resemble drift so much as drive (Gutz and Leslie, 1976). It could also be regarded as a form of gamete-level selection, just as meiotic drive can be so configured. However, BGC is different from any mode of selection that requires the allele to be advantageous to the bearer of the allele, be that bearer a haploid gamete or the diploid parent/progeny. It is indeed substantially different from certation in which the allele for which $k>0$ applies is one that makes the pollen bearing it competitively better. Similarly, in cases of meiotic drive where the driving chromosome "kills" the sperm bearing the driven against one (as in *SD* in *Drosophila*), one can see the drive allele as giving the sperm bearing it an advantage when in competition against the sperm from the same male not carrying the drive allele. As regards the neutralist-selectionist debate I think it best to consider BGC neither neutralist nor selectionist, and hence that it best considered a third class of model.

It is striking that the literature on BGC and that on selfish elements rarely cross reference each other even though the underlying logic is the same (for an exception see Werren, 2011). One reason for this is that unlike meiotic drive genes (*SD*, *t*-complex, spore killers), there is nothing sophisticated about the allele whose transmission is being affected that renders its transmission distorted: the sophistication is all in the biology of the repair complexes that have evolved the bias.

**Is biased gene conversion important in all eukaryotes: A problem with biased technology?**

In many species the extent of the bias in biased gene conversion is strong, with ~70:30 bias not being unusual at the site of conversion events. However, is biased gene conversion universal and this strong? The best data derives from Mancera et al.'s array-based study in yeast (Mancera *et al*, 2008) in which a bias is observed but it is modest at just 50.6% in favour of GC. We recently tried to replicate this using whole genome sequencing rather than using an array-based method (Liu *et al*, 2017). We found that if anything the bias is slightly the other way (50.7% in favour of AT alleles). It is perhaps striking that the two methods agree to within about 1%. Unfortunately, this is not good enough as the two estimates sit on either side of the key 50:50 threshold. If we merge the two (a sample of over 100,000 AT<->GC conversion events) there is no significant net bias (50.03% in favour of GC). Making matters worse, owing to the large sample sizes in both studies,

the two estimates of bias are significantly different. What is going on? The strains in both instances here were the same, and between strain differences don't seem especially strong (Liu *et al*, 2017). A possible problem then is a difference in technology: arrays in Mancera et al. versus whole genome sequencing. Both have recognised biases (see e.g. Benjamini and Speed, 2012; Lam *et al*, 2012; Rieber *et al*, 2013; Serhal and Lemieux, 2013; Uchida *et al*, 2005; Winchester *et al*, 2009). SNP arrays for example are thought to be >99% accurate (LaFramboise, 2009), which may sound impressive but even a 1% error rate can easily interfere with estimation of a very weak bias. While we validated a subsample of our calls via Sanger sequencing and found no issues, we still don't know the cause of the difference and it is notable that a further recent analysis using the closely related species *Saccharomyces paradoxus* finds a very weak and barely significant bias in favour of GC (Liu *et al*, 2018). However, as this example shows, when we are looking for miniscule biases then method bias might start to become so prominent that we will need to do more than just sequence more.

**Do weak biases matter: the missing concept of the effectively Mendelian allele?**

If the bias is of the order of a tiny deviation from 50:50 would this matter? Put differently, my assertion above that $k$ must be *exactly* zero might not be correct. In population genetics there is the concept of the effectively neutral allele. This is a Mendelian allele whose effects on fitness are so small that the fixation rates of such alleles are effectively the same as an allele with no effects on fitness, i.e. a strictly neutral allele. Classically, if $s$ is the selective effect of an allele, then if $s<<1/2N_e$ it will be effectively neutral, where $N_e$ is the effective population size. In the same context we can consider the effectively Mendelian allele. This would be a neutral allele whose transmission advantage ($k$) is so small that it behaves as if it were a Mendelian neutral allele. This is a term that, I would suggest, is needed but never employed to the best of my knowledge.

Mathematically we are not completely in the dark about such a concept. Consideration of biased gene conversion has noted the mathematical resemblance to positive selection (Nagylaki, 1983) and extension of diffusion models have permitted estimation of equilibrium GC content under additive assumptions incorporating biased gene conversion (Marais *et al*, 2004). This direct correspondence between biased gene conversion and weak positive selection is in many regards bad news for the technology bias. A bias as small as 50.03: 49.97 could in a selectionist framework be considered an allele under strong selection, so long as the effective population size is great enough and gene conversion acts on the site regularly enough. For a regularly sexual species with

effective population sizes in the millions, a utterly miniscule net bias from 50:50 could behave as if non-neutral. Good luck trying to detect that!

**Discussion**

While absence of bias in segregation ratios was key to the understanding that selection as a force can matter, a century later focus has to some degree shifted to the possibility that biased segregation matters, especially for processes like biased gene conversion. As I have argued, however, resolving subtle but biologically important biases puts us ever closer to the limits of technology, owing to their intrinsic biases. The centrality of transmission bias (or lack thereof) to understanding the fate of alleles also underpins the more general notion that to understand evolution, we need to understand the underlying transmission genetics, which in turn requires us to understand molecular genetics (for example the molecular biology of gene conversion).

To some extent the last century was one in which understanding of transmission and population genetics predominated in the pre-DNA era, whilst molecular biology was immensely successful in the post DNA era. But, I would suggest, while there certainly has been interaction between molecular and population genetics, not least through population and evolutionary genetical analysis of sequence data, they have not had as much to say to each other as they might have, perhaps owing to the usual ghettoization of academic disciplines. Evolutionary biologists have much to learn from really understanding the black box of molecular genetics. The example of biased gene conversion is a case in point. This would be an example where the assumption that one can just study phenotype and ignore the underlying genetics – the phenotypic gambit (Grafen, 2014) – fails (see also Hadfield *et al*, 2007)). Equally, those that study the basics of molecular biology and molecular genetics can similarly enrich their understanding through appreciation of the nuances of population and evolutionary genetics. For example, acknowledging that species with small populations are expected to have bloated error-prone genomes (Lynch and Conery, 2003), simply because selection is inefficient when $N_e$ is low, can add a necessary caution to a potentially futile search for a function for all things. Now more than ever these distinct disciplines could benefit from sitting more closely under one umbrella, with biases about the value of one subject area over the other left to the side.

**Bias and pedagogy**

What in broader scope are we to make of this history? To those of us evolutionary biologists wedded to genetics, it seems quite trivial that you cannot fully understand evolution without an

understanding of genetics. And yet, in UK schools the two subjects are taught as distinct entities with no connection (selection alone matters and the phenotypic gambit is implicitly made). So surprised was I to discover this that we set up a large scale randomised control trial to examine the role of teaching order in secondary schools (Mead *et al*, 2017). Some classes were taught evolution then genetics, the others genetics then evolution. Teaching genetics before evolution led to no diminution of genetics understanding (compared to the other way around) but improved evolution understanding 5-10% compared with teaching in the opposite order (Mead *et al*, 2017).

One hypothesis to explain why teaching genetics first is so successful is that a grounding in genetics renders evolution a logical necessity, so making it easier to understand as a process: if you understanding DNA, you can understand mutations and hence alleles, if you understand alleles you understand that they can change frequency and hence that populations can genetically change over time. If so, then reinforcing the multiple different reasons that alleles might change frequency (neutral evolution, classical selection, biased transmission) should help solidify the connection between DNA, mutation and evolution and in turn, the inevitability of genetical change of populations. Teaching the importance of biased and unbiased transmission may then be an effective means to breakdown psychological biases that cause cognitive dissonance so impeding learning about evolution (Lawson and Worsnop, 1992; McKeachie *et al*, 2002), although the importance of this may vary between the US and the UK (Mead *et al*, 2018). This remains to be tested, but we know that when students learn effectively about evolution their acceptance of evolution (different from their understanding of evolution) also goes up (Mead *et al*, 2017), suggesting, optimistically, that better understanding has some role in dissolving bias.

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